JPPT | Single-Center Retrospective Study

Comparative Effectiveness of Dual- Versus Mono-Sedative Therapy on Opioid Administration, Sedative Administration, and Sedation Level in Mechanically Ventilated, Critically Ill Children

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OBJECTIVE We estimated the effect of early initiation of dual therapy vs monotherapy on drug administration and related outcomes in mechanically ventilated, critically ill children.

METHODS We used the electronic medical record at a single tertiary medical center to conduct an active comparator, new user cohort study. We included children <18 years of age who were exposed to a sedative or analgesic within 6 hours of intubation. We used stabilized inverse probability of treatment weighting to account for confounding at baseline. We estimated the average effect of initial dual therapy vs monotherapy on outcomes including cumulative opioid, benzodiazepine, and dexmedetomidine dosing; sedation scores; time to double the opioid or benzodiazepine infusion rate; initiation of neuromuscular blockade within the first 7 days of follow-up; time to extubation; and 7-day all-cause in-hospital death.

RESULTS The cohort included 640 patients. Children receiving dual therapy received 0.03 mg/kg (95% CI, 0.02–0.04) more dexmedetomidine over the first 7 days after initiation of mechanical ventilation than did monotherapy patients. Dual therapy patients had similar sedation scores, time to double therapy, initiation of neuromuscular blockade, and time to extubation as monotherapy patients. Dual therapy patients had a lower incidence of death.

CONCLUSIONS In this study, initial dual therapy compared with monotherapy does not reduce overall drug administration during mechanical ventilation. The identified effect of dual therapy on mortality deserves further investigation.

ABBREVIATIONS EHR, electronic health record; ICU, intensive care unit; PIM 3, Pediatric Index of Mortality 3; RESTORE, Randomized Evaluation of Sedation Titration for Respiratory Failure; SBS, State Behavioral Scale

KEYWORDS critically ill children; dual therapy; mechanically ventilated children; monotherapy; sedation level

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Introduction

Respiratory failure is the most common reason for admission to the pediatric intensive care unit (ICU), accounting for up to 30% of all admissions.[1] Invasive mechanical ventilation can be a lifesaving therapy for infants and children with respiratory failure.[2] Nevertheless, pain and anxiety are common experiences during mechanical ventilation[3–5] and are associated with increased hemodynamic instability,[6] microvascular oxygen consumption,[7] immunosuppression,[8,9] posttraumatic stress disorder, and reduced health-related quality of life after ICU stay.[10] To reduce risks for these complications, critically ill children supported by mechanical ventilation often receive sedatives and analgesics; however, such use in excess of the minimum amount needed may also contribute to potential harm.[11] Increased exposure to sedatives and analgesics is associated with adverse outcomes such as elevated drug tolerance, iatrogenic withdrawal syndrome, delirium, debility, prolonged ICU and hospital stays, and higher overall health care costs.[12,13]

In adults, methods supporting light or no sedation[14] have resulted in shortened durations of mechanical ventilation, ICU stays, and hospital stays, as well as decreased delirium and long-term cognitive dysfunction.[15,16] These strategies have included primary administration of analgesia, daily sedation interruption, and titration of sedation to a specific goal.[16,17] Yet evidence for similar approaches in children is inconsistent, with some evidence suggesting increased risk for adverse

events;[18,19] because children may become frightened and are not as easily redirected as adults, deeper levels of sedation are often needed. Drug tolerance risks escalate with increasing drug duration, so sedation or analgesia goals are difficult to achieve once a patient has demonstrated inadequate sedation or pain control.[20,21] Hyperalgesia resulting from prolonged, uncontrolled acute pain can be exacerbated by further administration of opioids.[21] Initiation of dual drug therapy instead of monotherapy permits pharmacodynamic synergy and may allow sedation goals to be reached while limiting overall drug exposure and sequelae; however, such a strategy has not previously been evaluated in children. We sought to use real-world data to estimate the effect of initial dual therapy compared with single drug administration (monotherapy) on cumulative drug exposure and related outcomes in mechanically ventilated children. We hypothesized that initial dual drug therapy would be associated with improved outcomes.

Materials and Methods

Overall Study Design. We conducted an active comparator, new user cohort study of the effectiveness of initial administration of dual compared with single drug therapy for facilitating sedation and analgesia while limiting total sedative and analgesic exposure in mechanically ventilated, critically ill children.

Data Source. We used electronic health records (EHRs) from Duke University Medical Center, a tertiary care facility, as the primary source of data. Data on patient diagnoses, drug administration, laboratory studies, ICU and hospital length of stay, and patient outcomes of interest were extracted from the EHR. In particular, details about intubation and mechanical ventilation were extracted from intubation logs and respiratory flowsheets within the EHR. Data were then stored in the Protected Analytics Computing Environment for management and analyses.

Study Population. We identified all children <18 years of age at the time of hospital admission, admitted to the Duke Pediatric ICU or Pediatric Cardiac ICU between July 1, 2013, and December 31, 2018, and undergoing their first course of mechanical ventilation for the hospital stay. The start date of the study coincides with the adoption of Epic Systems (electronic medical record system) at Duke University, enabling data extraction as detailed above. For inclusion in the analysis cohort, patients undergoing surgery had to be admitted to the ICU from the operating room within 6 hours of intubation for surgery; if transferred from an outside hospital, patients had to reach Duke Hospital within 6 hours of intubation (Supplemental Figure S2). Patients intubated in the Duke Emergency Department are always admitted to the pediatric ICU within an hour of intubation, so we did not explicitly hold patients from the Duke Emergency Department to this same time criterion. Also, patients had to be exposed to a bolus dose or continuous infusion of at least one of the following sedatives or analgesics within 6 hours after intubation: midazolam, dexmedetomidine, fentanyl, lorazepam, diazepam, methadone, hydromorphone, morphine, ketamine, clonidine, propofol, or pentobarbital (Supplemental Figure S2).

We excluded patients meeting any of the following criteria: 1) admitted from an outside hospital without a documented date and time of intubation; 2) courses of mechanical ventilation lasting less than 6 hours; 3) initially mechanically ventilated via tracheostomy, owing to minimal sedation requirements in this setting compared with mechanical ventilation via endotracheal tube; 4) prevalent use of sedatives or analgesics of interest; or 5) without documented dosing weight (for weight-based dosing of sedatives/analgesics) from the time of hospital admission through 6 hours (inclusive) after intubation. We defined prevalent use of sedatives or analgesics of interest according to whether or not a patient had either exposure to continuous infusions of drugs of interest or more than a single bolus dose of drugs of interest during the washout period. We defined the washout period starting 12 hours prior to intubation and ending at 30 minutes prior to intubation to account for the pharmacokinetics of most sedatives and analgesics in children, where plasma concentrations are expected to be minimal >10 hours after the last dose of drug (Supplemental Figure S2). We excluded the 30 minutes prior to intubation because sedatives and analgesics are commonly administered to facilitate intubation, and to account for some uncertainty regarding the exact timing of intubation; our definition relies on documentation from nursing and respiratory therapists, which may be slightly inaccurate depending on circumstances surrounding the patient (e.g., extreme illness). For patients intubated at an outside hospital, in the Duke Emergency Department, or at the time of admission to the hospital, for whom we could not observe the entire washout period but who otherwise met inclusion and exclusion criteria, we assumed that there was no exposure to sedatives or analgesics of interest during the washout period and that these subjects could remain in our sample.

Definitions. ***Intubation and Extubation.*** We defined the time of intubation as the time documented on the intubation log for the first course of mechanical ventilation (Supplemental Methods). We identified the time of extubation as the first time after intubation with documentation of an oxygen device (Supplemental Methods).

Dual or Mono Drug Therapy. We defined a patient as exposed to dual therapy or monotherapy from the number of continuous infusions during the treatment period, with 1 exception: patients exposed to a single infusion, but 2 or more bolus doses of a second sedative or analgesic, were classified as receiving dual

therapy. Bolus doses could have been administered per a schedule or as needed.

Dosing Outliers. We converted all bolus doses to mg/kg and continuous infusions to mg/kg/hr. To facilitate evaluation of dosing by drug class, we also converted doses of opioids to morphine equivalents and doses of benzodiazepines to lorazepam equivalents (Supplemental Table S1).

We evaluated the distribution of drug dosing for each included sedative and analgesic and identified all doses that were larger than the 99.99th percentile for that drug. From prior knowledge and review of these extreme doses by 2 independent clinicians, we believe these outliers largely represent errors in data entry, primarily related to misplacement of decimal points. We then systematically replaced these doses by a dose equivalent to one-tenth of the original value.

Study Outcomes. We identified the following primary outcomes of interest: cumulative dose per kilogram of body weight of 1) opioids; 2) benzodiazepines; and 3) dexmedetomidine for the first 7 days. Secondary outcomes included 1) the mean of the median daily sedation score (State Behavioral Scale [SBS]) for the first 7 days; 2) the time to double the mean hourly opioid or benzodiazepine infusion rate (mg/kg/hr) from the first 12 hours of the study period (6 hours post intubation through 18 hours post intubation); 3) whether neuromuscular blockade was initiated (i.e., administration of bolus dose or start of an infusion) within the first 7 days; 4) time to extubation; and 5) all-cause, 7-day, in-hospital mortality. All outcomes were assessed from the end of the treatment period (e.g., 6 hours after intubation). In a *post hoc* analysis, we also evaluated the number of days of exposure to neuromuscular blockade within the first 7 days of mechanical ventilation.

For outcomes of cumulative exposure and sedation level, we also assessed outcomes through 7 days after the end of the treatment period. For time-to-event analyses, children who died prior to the end of follow-up were right-censored.

Covariates. From review of the literature and clinical expertise, we developed a causal-directed acyclic graph[22] and identified the following minimally sufficient confounder adjustment sets for estimating the total effect of initial dual therapy compared with monotherapy on both primary and secondary outcomes: age, initial diagnosis, race, severity of illness, sex, year, and time of year.[23] We defined severity of illness according to the patient's probability of mortality as defined by the Pediatric Index of Mortality 3 (PIM 3) score.[23] This score was calculated from laboratory data available within 1 hour prior to ICU admission through 1 hour after admission, and non-laboratory components (e.g., pupillary reaction) available closest to the time of ICU admission and occurring within 1 hour after ICU admission.

Statistical Analysis. We used descriptive statistics to summarize baseline characteristics of the entire cohort and each treatment group. We explored the distribution of patient characteristics by baseline probability of death and age categories, which were determined *a priori* to be potential effect measure modifiers. We used graphical representations and summary statistics to evaluate the distribution of crude outcomes. We summarized data for the entire cohort and treatment group. We reported summary measures of means ± SDs or medians (25th and 75th percentiles) based on distribution of the data.

We used stabilized inverse probability of treatment weighting to standardize covariates between treatment groups. We then used descriptive statistics to estimate the average treatment effect for each of the study outcomes in the weighted cohorts and quantile regression to estimate the difference in medians between the 2 groups. We used differences in medians owing to the highly skewed distribution of drug administration data. From observed differences in covariate distribution between dual therapy and monotherapy patients within subgroups of age and baseline probability of death, we repeated the process of standardizing covariates within these subgroups. We then conducted stratified analyses to explore effect measure modification by age and probability of death category. We also conducted a sensitivity analysis to evaluate the incidence of all-cause, in-hospital death. STATA 16 (StataCorp LLC) was used for all analyses. We determined all analyses *a priori* on the basis of relevance to clinical care, and all results are presented herein; therefore, we did not correct for multiple comparisons.

Results

Description of Study Cohort. We identified 640 patients who met inclusion and exclusion criteria (Supplemental Figure S1), including 269 patients who received monotherapy and 371 patients who received dual therapy during the treatment period. On average, patients receiving monotherapy were slightly younger, more likely to have been intubated in the year 2016 or after, more likely to have been admitted from an outside hospital, had a higher probability of death at the time of admission, and less commonly had a cardiac diagnosis. Nevertheless, differences between groups were minimal (Supplemental Table S2).

Main Analysis. The distribution of drug dosing over the first 7 days of evaluation was markedly skewed in the study population, with the mean administration of opioids, benzodiazepines, and dexmedetomidine far exceeding the median value for each of these drug classes. We identified no difference in crude (i.e., unadjusted for confounders) median administration of opioids or benzodiazepines; however, dual therapy patients received 0.03 mg/kg (95% CI, 0.02–0.04) more dexmedetomidine than did monotherapy patients (Table 1). There were no substantial differences in crude

Table 1. Opioid, Benzodiazepine, and Dexmedetomidine Administration by Dual Therapy vs Monotherapy Over the First 7 Days After Treatment Period

	Median Dual Therapy (25th, 75th Percentiles)	Median Monotherapy (25th, 75th Percentiles)	Difference in Medians* (95% CI)
Opioids, mg/kg			
Crude	12.34 (2.70, 40.0)	11.48 (2.88, 34.2)	0.86 (−3.69 to 5.41)
Adjusted	12.03 (2.70, 39.8)	11.13 (3.07, 34.1)	0.89 (−3.59 to 5.38)
Benzodiazepines, mg/kg			
Crude	0.12 (0, 1.22)	0.050 (0, 0.38)	0.075 (−0.0045 to 0.154)
Adjusted	0.11 (1.03, 12.6)	0.062 (0, 0.44)	0.050 (−0.020 to 0.121)
Dexmedetomidine, mg/kg			
Crude	0.017 (0.0010, 0.081)	0.0023 (0, 0.021)	0.015 (0.0075–0.022)
Adjusted	0.017 (0.0010, 0.077)	0.0018 (0, 0.017)	0.015 (0.0080–0.023)

* Difference in medians obtained by using quantile regression methods.

median sedation scores between the groups over the follow-up period, nor was there a difference in initiation of neuromuscular blockade during the first 7 days. Children receiving initial dual therapy compared with monotherapy were more quickly extubated (median, 63 hours [22, 444] vs 78 hours [26, 666]) and less likely to die within the first 7 days of mechanical ventilation (4/371 [1%] vs 9/269 [3%]).

Covariate Standardization. Application of inverse probability of treatment weighting resulted in a final cohort of 622 patients (Supplemental Table S2). For those with baseline probability of death ≤3% and >3%, weighting improved many differences in distribution between dual therapy and monotherapy patients; however, differences remained with sex distribution and intubation time of day, particularly for those with a probability of death >3%. Weighting did not notably improve differences in characteristic distribution within the lowest and highest age groups. Nonetheless, standardized mean differences between groups met standard criteria of ≤ ±0.1 for all covariates.

Effect of Dual Therapy Compared With Monotherapy in Weighted Population. After weighting, participants receiving initial dual therapy were administered more dexmedetomidine over the first 7 days than those receiving monotherapy (median difference, 0.015 mg/kg [95% CI, 0.008–0.023]). We identified no differences between groups in receipt of opioids or benzodiazepines among those receiving initial dual therapy compared with monotherapy (Table 1). We noted no differences between groups in the following outcomes: time to double opioid or benzodiazepine dose (median difference, 5.5 hours [95% CI, −17.2 to 28.3]) compared with the first 12 hours after intubation; median daily SBS scores (both group medians [25th, 75th percentiles]: 0 [−1, 0]); or initiation of neuromuscular blockade within the first 7 days of the follow-up period (dual: 45.1% [95% CI, 39.8–50.3]; mono: 43.9% [95% CI, 37.8–50.1]). Dual therapy did not result in reduced duration of mechanical ventilation (−8.92 hours [95% CI, −34.18 to 16.35]) when compared with monotherapy. Patients receiving dual therapy had a lower incidence of death (dual: 0.9% [0.2–2.4]; mono: 4.6% [2.4–7.9]; difference, −3.7% [95% CI, −6.8 to −1.2]) (Supplemental Table S3). We identified no differences between groups in the number of days of exposure to neuromuscular blockade; monotherapy patients received 1.32 ± 1.97 (mean ± SD) days of neuromuscular blockade, while dual therapy patients received 1.33 ± 1.96 days of neuromuscular blockade.

Sensitivity Analysis. On sensitivity analyses, patients receiving dual therapy had a lower incidence of death prior to hospital discharge (dual: 8.5% [5.9–12]; mono: 14.6% [10.5–19.4]; difference, −5.9% [95% CI, −11 to −0.7]).

Description of Subgroups. When evaluating the distribution of dual therapy and monotherapy among the subgroup of children with a baseline probability of death ≤3%, we found that patients receiving monotherapy were more commonly male than those who received dual therapy. Among the subgroup of children with a probability of death >3%, monotherapy patients were more commonly <1 month of age, female, White, intubated during the daytime, and intubated during the year 2015 or later (Supplemental Table S4). When evaluating the distribution of dual therapy compared with monotherapy among subgroups of age, we found differences in dual therapy and monotherapy by sex, race, and ethnicity. Among those <1 month of age, monotherapy recipients were also more commonly intubated during the night shift and admitted from an outside hospital in comparison to dual therapy patients, while monotherapy patients who were 12 to <18 years of age were more commonly admitted from an operating room rather than the general floor or another location (e.g., the emergency department) in comparison to dual therapy patients (Supplemental Table S5).

Effect Measure Modification. We evaluated each of the primary and secondary outcomes by initial

probability of death subgroup and by age subgroup. There was differential administration of dexmedetomidine by initial probability of death. Among those who had an initial probability of death ≤3%, dual therapy patients were administered 0.022 mg/kg (95% CI, 0.01–0.03) more dexmedetomidine than monotherapy recipients. Among those who had an initial probability of death >3%, no differences in dexmedetomidine administration were noted between the dual therapy and monotherapy groups (median difference, 0.007 mg/kg; 95% CI, −0.003 to 0.017). We identified no differences in opioid or benzodiazepine administration by probability of death subgroup (Table 2). Similarly, those <1 month of age in the dual therapy group were administered 0.04 mg/kg (0.02–0.06) more dexmedetomidine than those receiving initial monotherapy. Nevertheless, no other subgroup noted differences in dexmedetomidine administration by dual therapy compared with monotherapy, nor did any age subgroup experience differences in opioid or benzodiazepine administration according to initial dual therapy or monotherapy (Table 3).

We identified no differences in SBS scores, doubling time, or initiation of neuromuscular blockade by dual therapy or monotherapy administration, within baseline probability of death or age subgroups. Among children with a baseline predicted probability of death >3%, dual therapy resulted in decreased duration of mechanical ventilation by 62 hours (95% CI, −119.3 to −5.2), whereas no difference was noted among those with an initial probability of death ≤3%. We also noted no differences in death between dual therapy and monotherapy within any of the age subgroups. In all subgroups, incidence of death was lower among those receiving dual therapy (Supplemental Table S3).

We did observe some differences in incidence of death by baseline probability of death; among

Table 2. Drug Administration Stratified by Baseline Probability of Death Category

	Median Monotherapy (25th, 75th Percentiles)	Median Dual Therapy (25th, 75th Percentiles)	Difference in Medians (95% CI)
Opioids, mg/kg			
≤0.03 (n = 372)	7.61 (1.54, 29.2)	12.4 (2.68, 35.5)	4.76 (−0.323 to 9.84)
>0.03 (n = 250)	15.5 (4.21, 40.4)	11.7 (2,75, 39.4)	−3.82 (−12.3 to 4.64)
Benzodiazepines, mg/kg			
≤0.03 (n = 372)	0.0484 (0, 0.200)	0.106 (0, 0.818)	0.058 (−0.0146 to 0.130)
>0.03 (n = 250)	0.105 (0, 1.68)	0.149 (0, 1.17)	0.0440 (−0.178 to 0.266)
Dexmedetomidine, mg/kg			
≤0.03 (n = 373)	0.00221 (0, 0.017)	0.0239 (0.00221, 0.0790)	0.0217 (0.0105–0.0329)
>0.03 (n = 250)	0 (0, 0.0174)	0.00878 (0, 0.0596)	0.00878 (0.00116–0.0164)

Table 3. Drug Administration, Stratified by Age Group

	Median Monotherapy (25th, 75th Percentiles)	Median Dual Therapy (25th, 75th Percentiles)	Difference in Medians (95% CI)
Opioids, mg/kg			
<1 mo (n = 179.8)	16.3 (7.6, 34.1)	18.1 (9.8, 40.2)	1.78 (−6.28 to 9.85)
1 mo to <2 yr (n = 197.1)	21.1 (4.23, 43.1)	13.2 (3.67, 51.9)	−7.99 (−23.4 to 7.40)
2 to <12 yr (n = 160.2)	5.04 (1.24 , 17.0)	4.50 (1.31, 12.36)	4.72 (0.940–35.5)
12 to <18 yr (n = 85)	9.16 (2.18, 9.16)	4.72 (0.940, 35.5)	−4.44 (−16.0 to 7.13)
Benzodiazepines, mg/kg			
<1 mo (n = 179.8)	0.0274 (0, 0.219)	0.0435 (0, 0.294)	0.0161 (−0.0715 to 0.104)
1 mo to <2 yr (n = 197.1)	0.107 (0, 1.75)	0.353 (0, 1.74)	0.245 (−0.177 to 0.669)
2 to <12 yr (n = 160.2)	0.0556 (0, 0.308)	0.105 (0, 1.17)	0.0497 (−0.135 to 0.235)
12 to <18 yr (n = 85)	0.149 (0.0217, 19.6)	0.0789 (0, 0.479)	−0.0697 (−15.6 to 15.5)
Dexmedetomidine, mg/kg			
<1 mo (n = 179.8)	0.00294 (0, 0.0329)	0.0431 (0.00700, 0.0900)	0.0402 (0.0180–0.0624)
1 mo to <2 yr (n = 197.1)	0.00886 (0.00027, 0.0280)	0.0235 (0.00393, 0.0936)	0.0146 (0 to −0.00590)
2 to <12 yr (n = 160.2)	0 (0, 0.00421)	0.00301 (0, 0.261)	0.00301 (−0.000481 to 0.00649)
12 to <18 yr (n = 85)	0 (0, 0.00616)	0.00204 (0, 0.0537)	0.00204 (−0.0144 to 0.0185)

children with a low baseline predicted probability of death (≤3%), dual therapy resulted in a decreased incidence of death when compared with monotherapy (difference, 8.6%; 95% CI, −14.9 to −2.3). No such differences were observed for those with a baseline predicted probability >3% or any subgroup involving children <12 years of age. Among children 12 to <18 years of age, we observed increased incidence of death among those receiving dual therapy compared with monotherapy (difference, 15.6%; 95% CI, 0.4–30.8).

Discussion

We leveraged data from EHRs to investigate the relationship between a specific strategy of sedative and analgesic administration: initial dual therapy compared with monotherapy in mechanically ventilated, critically ill children. Overall, we identified greater variability within groups than between groups. We found that initial dual therapy resulted in increased administration of dexmedetomidine over the first 7 days after intubation, driven by administration among those with a lower probability of death or <1 month of age. Initial dual therapy did not result in differences in opioid or benzodiazepine administration, sedation scores, time to double opioids or benzodiazepines, or initiation of neuromuscular blockade. We observed no overall effect of dual therapy compared with monotherapy on duration of mechanical ventilation. Additionally, we observed lower incidence of 7-day, in-hospital death among those receiving dual therapy compared with monotherapy.

The observed administration of dexmedetomidine among those with dual therapy compared with monotherapy suggests that dexmedetomidine is largely used as adjunct therapy in mechanically ventilated, critically ill children and is rarely administered as monotherapy. Dexmedetomidine has some analgesic properties[24] but is not generally sufficient to treat pain associated with the endotracheal tube. We found no difference in opioid or benzodiazepine administration between initial dual therapy compared with monotherapy; this is contrary to our original hypothesis, which was that there would be reduced overall drug exposure with dual therapy owing to a synergistic effect of the drugs in inducing sedation. The point estimates actually suggest a trend towards increased administration of benzodiazepines and opioids among those initially administered dual therapy compared with monotherapy. We observed this trend despite very similar SBS scores between dual therapy and monotherapy patients and a trend towards longer time to doubling opioid or benzodiazepines among those initially receiving dual therapy. Potential reasons for these findings include 1) escalation of drug motivated by something other than sedation scores; 2) poor sensitivity of the SBS scoring system to identify true differences in sedation state in real-life settings; 3) lack of synergistic effect of drugs; or 4) drug tolerance potentially occurring much more quickly than previously believed. Nonetheless, the lack of difference in exposure to opioids and benzodiazepines is also consistent with the largest known study to date that investigated a specific, nurse-driven sedation protocol vs usual care at 31 North American pediatric ICUs.[25]

According to our hypothesis, opioid exposure may mediate the relationship between duration of mechanical ventilation and initial therapy. Opioids suppress respiratory drive and often require additional intubation time to wean to a more tolerable dose prior to removal of the breathing tube. Those administered larger doses of opioids would likely take more time for weaning and, therefore, require more prolonged periods of mechanical ventilation. Consistent with these ideas, we observed a shorter duration of mechanical ventilation and a trend towards reduced administration of opioids among those with a baseline predicted probability of death >3% who received dual therapy vs monotherapy. Such findings have not been previously identified in the pediatric literature; the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study did not identify a shorter duration of intubation associated with the nurse-driven sedation protocol compared with usual care.[25] However, in adults, retrospective studies and randomized trials suggest that methods such as primary administration of analgesia and titration of sedation[17] to a specific goal have resulted in shortened durations of mechanical ventilation.[16]

We noted a lower risk of observed 7-day, in-hospital death among those receiving dual therapy compared with monotherapy overall and across all subgroups. The potential mechanism underlying this finding remains unclear. One possible explanation that could not be explored within this investigation, owing to missing data on delirium scores, is that dual therapy is associated with reduced risk of delirium in this subgroup. Prior studies in both children and adults have identified an association between delirium and mortality in the critically ill patient.[26–29] Alternatively, this finding could be due to chance, but still deserves further investigation.

Our study had several limitations. First, this investigation uses the EHR, which is designed for administrative billing as opposed to research, thereby potentially limiting the accuracy of some data points. Specifically, we observed missing or incorrect data for some entries regarding the time of intubation and extubation, and likely errors were identified with regard to dosing. These missing data points or errors required us to make some assumptions and create rules and definitions to account for these issues, including imputation, which could influence study results, despite the rules being systematically applied to minimize the risk of bias. Second, owing to data limitations, we could not evaluate out-of-hospital mortality, which may contribute to bias in our estimates of mortality. Third, we had a limited

sample size and fairly strict definitions required for inclusion, limiting external validity, especially to those admitted from an outside hospital. Fourth, although our analyses used weighting and we achieved balance with most of the covariates, some residual differences in subgroups remained, leaving room for uncontrolled confounding that could have contributed to our results. Fifth, due to limited documentation, we could not account for the target SBS scores in our analysis, although most (>90%) patients typically have an understood target score of −1. Finally, we could not account for specific patient characteristics that may have prompted administration of dual therapy compared with monotherapy and influenced study outcome.

Conclusion

This is the first analysis to examine the specific strategy of initial dual therapy compared with monotherapy for sedation and analgesia in mechanically ventilated, critically ill children. We identified new areas of possible investigation, as well as highlight the challenges in identifying the optimal strategy to maximize pediatric patient comfort while minimizing adverse effects during mechanical ventilation.

Article Information

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